

WHAT IS CLAIMED:

1. A protein comprising an immunoglobulin heavy chain (HC) variable domain sequence and an immunoglobulin light chain (LC) variable domain sequence, wherein the HC variable domain sequence and the LC variable domain sequence form an antigen binding site that binds to an activated conformation of LFA-1, wherein the protein has one or more of the following properties:
 - 5 (i) the heavy chain variable domain sequence comprises:
 - (a) a CDR1 that comprises at least 3 amino acids from RYVMW (SEQ ID NO:1)
 - 10 (b) a CDR2 that comprises at least 13 amino acids from YIWPSGGNTYYADSVKG (SEQ ID NO:2); and/or
 - (c) a CDR3 that comprises at least 8 amino acids from SYDFWSNAFDI (SEQ ID NO:3);
 - (ii) the light chain variable domain sequence comprises
 - 15 (a) a CDR1 that comprises at least 7 amino acids from RASQSIGSYLN (SEQ ID NO:7);
 - (b) a CDR2 that comprises at least 4 amino acids from AASSLQS (SEQ ID NO:8); and/or
 - (c) a CDR3 that comprises at least 5 amino acids from QQSYSTPS (SEQ ID NO:9);
 - 20 (iii) the heavy chain variable domain sequence comprises a sequence at least 85% identical to the heavy chain variable domain sequence of the D2-57, DX-2001, C1-54, or P1-G10 antibody;
 - (iv) the light chain variable domain sequence comprises a sequence at least 85% identical to the light chain variable domain sequence of the D2-57, DX-2001, C1-54, or P1-G10 antibody;
 - 25 (v) the heavy chain variable domain sequence comprises a sequence encoded by a nucleic acid that hybridizes under stringent conditions to a sequence that encodes the heavy chain variable domain sequence of the D2-57, DX-2001, C1-54, or P1-G10 antibody;

(vi) the light chain variable domain sequence comprises a sequence encoded by a nucleic acid that hybridizes under stringent conditions to a sequence that encodes the light chain variable domain sequence of the D2-57, DX-2001, C1-54, or P1-G10 antibody; and/or

5 (vii) the protein competes with antibody D2-57, DX-2001, C1-54, or P1-G10 for binding to activated LFA-1.

2. The protein of claim 1 that comprises the CDR regions of the D2-57 antibody.

10 3. The protein of claim 1 wherein the heavy and light chain variable domain sequences are at least 90% identical to corresponding variable domain sequences of the D2-57 antibody.

4. The protein of any of claims 1 wherein at least 80% of the FR regions are identical to FR sequence from a human germline sequence or a FR sequence of D2-57, C1-54, or P1-G10.

15 5. The protein of claim 1 wherein the heavy chain variable domains sequence comprises Xa-S-X2-D-X4-X5-S-X7-A-X8-X9-X10-X11 (SEQ ID NO:4), and (i) Xa is S or N; (ii) X2 is Y or F; (iii) X4 is hydrophobic; (iv) X5 is W or R; (v) X7 is N or Y; (vi) X9 is Y or F; (vii) X10 is D, E or A; and (viii) X11 is any amino acid.

6. The protein of claim 1 that is not immunogenic in humans.

20 7. The protein of claim 1 that is a full length IgG antibody.

8. The protein of claim 1 that is an antigen binding fragment of an antibody, and does not include an Fc domain.

9. The protein claim 1 that has at least a 20-fold preference for binding to activated LFA-1 relative to inactivated LFA-1.

25 10. A protein comprising an immunoglobulin heavy chain (HC) variable domain sequence and an immunoglobulin light chain (LC) variable domain sequence, wherein

(i) the HC variable domain sequence and the LC variable domain sequence form an antigen binding site that binds to an activated conformation of LFA-1 (“aLFA-1”);

5 (ii) the protein inhibits ICAM-1 binding to LFA-1 on human peripheral blood mononuclear cells with an IC₅₀ of less than 5 nM.

11, A pharmaceutical composition that comprising the protein according to any of claims claim 1-10 and a pharmaceutically acceptable salt.

12. A method of treating or preventing inflammation or an inflammatory disorder, the method comprising:

10 administering the protein of claim 1 to a subject in an amount effective to treat or prevent the inflammation or the inflammatory disorder.

13. The method of claim 12 wherein the protein is administered at dosages less than 1 mg/kg per week, for at least 2 weeks.

15 14. The method of claim 12 wherein the subject has psoriasis or is predisposed to psoriasis.

15. The method of claim 14 wherein the subject has stable, plaque psoriasis.

16. The method of claim 12 wherein the subject has or is predisposed to a disorder that is caused at least in part by a T cell inflammatory response.

17. The method of claim 12 wherein the subject has or is predisposed to 20 rheumatoid arthritis.

18. A method of suppressing an immune response, the method comprising: administering the protein of 1 to a subject in an amount effective to suppress an immune response of the subject.

19. The method of claim 18 wherein the subject has or is about to receive a 25 transplant.

20. The method of claim 18 further comprising administering a second agent that modulates T-cell function.

21. The method of claim 20 wherein the second agent that modulates T-cell function is an antibody to CD154 or an antibody to CD45RB.

22. A method of treating or preventing a disorder in a subject, the method comprising:

5 identifying a subject in need of an anti-LFA-1 antibody that preferentially binds to the activated form of LFA-1, but which subject does not respond or tolerate an anti-LFA-1 antibody that binds to activated and non-activated LFA-1 protein with substantially the same affinity; and

10 administering the anti-LFA-1 antibody that preferentially binds to the activated form of LFA-1, to the subject.

23. A method of modulating aLFA-1 activity, the method comprising:

providing an aLFA-1-binding protein of claim 1; and

contacting the protein to aLFA-1, in an amount sufficient to modulate aLFA-1 activity.

15 24. The method of claim 23 wherein the contacting is in vitro.

25. The method of claim 23 wherein the contacting is in vivo.

26. The method of claim 23 wherein the protein is contacted to aLFA-1 in the vicinity of a neoplastic cell.

20 27. The method of claim 23 wherein the protein is contacted to aLFA-1 in the vicinity of an endothelial cell.

28. A method for detecting the presence of an aLFA-1 protein, in a sample, in vitro, the method comprising:

25 (i) contacting the sample with an aLFA-1-binding protein according to any of claims 1-10, under conditions that allow interaction of the aLFA-1-binding protein and the aLFA-1 protein to occur; and

(ii) detecting interaction between the aLFA-1-binding protein, and the sample.

29. The method of claim 28 wherein at least one of the aLFA-1 binding protein or the aLFA-1 is immobilized.

30. A method for detecting the presence of activated LFA-1 in vivo, the method comprising:

5 (i) administering to a subject an aLFA-1-binding protein, under conditions that allow interaction of the aLFA-1-binding protein and the aLFA-1 protein to occur; and

10 (ii) detecting location of the aLFA-1-binding protein in the subject or formation of a complex between the aLFA-1-binding protein and aLFA-1 in the subject.

31. The method of claim 30 wherein the subject is a human subject.

32. The method of claim 30 wherein the detecting comprises imaging the subject.

15 33. The method of claim 30 wherein the aLFA-1-binding protein is labeled with an MRI detectable label.